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Development of wheezing in patients with cough variant asthma during an increase in airway responsiveness

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Development of wheezing in patients with cough variant asthma during an increase in airway responsiveness. Y.Y. Koh, J.H. Jeong, Y. Park, C.K. Kim. ©ERS Journals Ltd 1999.

ABSTRACT: Two theories explaining the mechanism for the manifestation of cough without wheeze in patients with cough variant asthma (CVA) are either a higher wheezing threshold or a milder degree of airway hyperresponsiveness. A significant proportion of patients diagnosed as having CVA eventually develop wheezing. The aim of this study was to investigate whether this change in the manifestation of asthma was associated with a decrease in wheezing threshold and/or an increase in airway hyperresponsiveness.

Thirty-six children (7–15 yrs) with CVA were prospectively studied for 4 yrs. Bronchial provocation tests with methacholine using the stepwise increasing concentration technique were performed annually to measure the provocative cumulative dose producing a 20% fall in forced expiratory volume in one second (PD_{20}). Wheezing thresholds were additionally determined at the initiation of and the end of the study (development of wheezing, or after 4 yrs).

Sixteen (Group 1) of 29 patients available for the follow-up developed clinical wheezing during the period; 13 patients (Group 2) stayed as CVA or their cough resolved. There was no significant change in wheezing thresholds from the initiation to the end of the study (Group 1: 40.9±8.2% *versus* 40.2±8.3%; Group 2: 41.4±7.1% *versus* 40.1±7.3%). Methacholine PD_{20} (geometric mean, range of 1 SD), expressed as breath unit (BU), significantly decreased in Group 1 patients as they developed wheezing (initial *versus* wheezing year: 60.8 BU, 29.2–126.5 *versus* 32.8 BU, 11.5–93.3; $p<0.01$), whereas the value did not change in Group 2 patients (initial *versus* after 4 yrs: 85.3 BU, 45.2–161.1 *versus* 84.3 BU, 39.7–179.1; NS).

The results suggest that an increase in airway hyperresponsiveness, but not a decrease in wheezing threshold, may have a pathogenetic role in the development of wheezing during the course of cough variant asthma in childhood.

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Cough variant asthma (CVA) is an occult form of asthma in which the only sign or symptom is chronic cough [1]. It is a common problem amongst all ages that frequently goes unrecognized, leading to underdiagnosis and undertreatment [2]. The main reason of underdiagnosis or delayed diagnosis in patients with CVA is thought to be a lack of wheezing detected by the patients and/or physician, because wheezing has long been considered the *sine qua non* of asthma [3].

Cough is an important part of the symptom complex in most asthmatic patients. Wheezing is a dynamic sign, occurring when flow through narrowed airways creates vibrations in the audible frequency [4]. In the investigation of the possible mechanism for the manifestation of cough without wheeze in patients with CVA, it has been demonstrated that they had a higher wheezing threshold (the minimal degree of airway obstruction when wheezing becomes audible) than those who report both cough and wheeze (classic asthma (CA)) [5]. Another theory for the manifestation is that CVA probably represents the milder end of the spectrum of asthma, reflecting a milder degree of airway hyperresponsiveness [1, 6]. Since variability of airflow obstruction is low in this circumstance, symptoms of airflow obstruction such as wheeze, are unlikely to occur [7].

Some studies have indicated that CVA may be a forerunner of CA [8, 9, 10]. HANNAWAY and HOPPER [9], and KONIG [10] found that typical attacks of wheezing developed in a significant number of children (80% and 75%, respectively) when followed for several months to 8 yrs. The current authors have also observed many patients with CVA, who began to wheeze within a few years after follow-up.

It was reasoned that the patients with CVA may represent a subset of asthmatics whose airways are less able to produce a wheeze and they may present as CA when the variable airway obstruction exceeds the threshold to generate wheeze. This may result from two concepts: firstly, the wheezing threshold may become reduced to a range of CA so that the variable airway obstruction can have a chance to produce audible wheezing; and, secondly, airway hyperresponsiveness may be enhanced during the course of CVA so that the increased variable airway obstruction can pass over the wheezing threshold. It was hypothetized that the development of wheezing in patients with CVA, *i.e.*, conversion to CA was associated with a

decrease in wheezing threshold and/or an increase in airway hyperresponsiveness. In order to test this hypothesis, children with CVA were prospectively studied, and the changes in wheezing threshold and methacholine reactivity were examined according to whether they developed wheezing.

Materials and methods

Thirty-six children with CVA were enrolled in the study. Initially, they were referred to the pulmonary clinic for the chronic cough, which had persisted for >2 months (range: 9 weeks to 2 yrs). The cough was usually dry or productive with scant amount of clear sputum and was mostly nocturnal. None of them had a wheeze nor a prolonged expiratory phase on physical examination. Normal results were found for the following tests: chest radiograph, spirometry, sinus films, and tuberculin skin tests. All patients responded significantly to a trial of oral theophylline 20–24 $mg \cdot kg \cdot day^{-1}$. All of them were recorded as having bronchial hyperreactivity (table 1). Skin-prick tests were performed, and atopy was defined by the presence of at least one positive reaction (>3 mm wheel diameter) with a battery of 15 common airborne allergens.

The prospective study was performed between December 1991 and February 1996. At the initiation of the study, bronchial provocation tests with methacholine were performed to measure bronchial reactivity and wheezing threshold. For the follow-up, patients were asked to attend the clinic every 3 months whenever possible, for clinical assessment and medication adjustment. At each attendance, patients were questioned about symptoms and signs in the interim, and a physical examination was performed if appropriate. Additional contact with each subject was made when wheezing was perceived by the patient or the patient′s parents for the first time. Wheezing was defined as a whistling sound coming from the chest but not the throat, which had been demonstrated in the procedure of the initial bronchial provocation test. The development of wheezing was documented in each individual when the claims of subjective wheezing were verified by a physician′s careful auscultation. In each calendar year, each patient was overall clinically assessed, and one of the three phases of symptom presentation was assigned: 1) wheezing phase, if an attack of wheezing was documented at any time during the last 12 months; 2) cough phase, if a patient had suffered from persistent cough for at least 2 weeks (occurring particularly at night, early in the morning or after exercise, with reduction after administration of bronchodilators); and 3) symptom-free phase, if a patient had experienced neither wheezing nor coughing. Methacholine reactivity was measured at the end of each year for all patients. In view of the fact that most of the atopic patients were sensitized predominantly to house dust mites, it was decided to perform the bronchial provocation test during the winter season (December to February) during which time the levels of house dust mites have been found to be the lowest and the least changing in South Korea [11].

Table 1. – Baseline characteristics of subject groups at the initiation of study

	Group 1	Group 2	Dropped-out
n	16	13	7
Mean age (Range) yrs	9.6 (7–14)	10.2 (7–15)	10.0 (8–13)
Sex M/F n	9/7	7/6	3/4
Atopy, n%	10 (62.5)	8 (61.5)	4 (57.1)
FEV_1 % predicted*	94.8±7.6	95.2±6.9	97.3±7.5
Initial bronchial provocation test			
Methacholine PD_{20} BU†	60.8 (29.2–126.5)	85.3 (45.2–161.1)	131.5 (88.1–196.3)
Wheezing threshold %*	40.9±8.2	41.4±7.1	38.1±6.3

Those patients who developed wheezing during the course of follow-up period were listed as Group 1; those who did not were listed as Group 2. *: mean±SD; †: geometric mean, and range of 1 SD in parenthesis. M: male; F: female; FEV_1: forced expiratory volume in one second; PD_{20}: provocative cumulative dose producing a 20% fall in FEV_1; BU: breath unit (1 BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine).

During the study, subjects were instructed to keep their cough symptom well controlled by minimum use of inhaled bronchodilators. They were asked to avoid major environmental changes, and if their parents were smokers, to keep their consumption constant. Those subjects who developed wheezing during the follow-up were treated with intermittent bronchodilator, and some of them were additionally given inhaled cromolyn sodium (n=6) or inhaled corticosteroid (n=4) according to the National Institutes of Health (NIH) guidelines [12]. The patients were brought to an end of the study by undergoing bronchial provocation tests for the measurement of methacholine reactivity and wheezing threshold at the end of the year of wheezing phase. Those subjects who did not develop wheezing used the same bronchodilator throughout the study. These patients were assessed annually for methacholine reactivity, and at the end of study (after 4 yrs of follow-up) for not only methacholine reactivity but also wheezing threshold.

For comparison of methacholine reactivity and wheezing threshold, a separate group of 13 patients with mild asthma (CA with wheezing history) were recruited. These patients underwent bronchial provocation test on one occasion.

High-dose methacholine inhalation tests were carried out using a modification of the method described by CHAI *et al.* [13]. Each patient attended for methacholine challenge at the same time of day on every occasion to avoid any circadian variation in reactivity [14]. All of the challenge tests were performed by a single investigator who was blinded to clinical status. All patients were asked to cease using inhaled bronchodilator or other medications 24 h, oral theophylline 48 h, and inhaled cromolyn sodium or inhaled corticosteroid 7 days, respectively, before the test. At the time of the test, all patients had been free of acute respiratory tract infection for 4 weeks. On each day of the test, lung function was measured in triplicates with a computerized spirometer (Microspiro-HI 298; Chest, Tokyo, Japan) after rests of 30 min between each test, and the study was continued only if the baseline forced expiratory volume in one second (FEV_1) was at least 70% of the predicted value [15]. The largest value of the triplicate FEV_1 at each time was used for analysis. The concentrations (0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, 25, 50, 100, 150 and 200 $mg \cdot mL^{-1}$) of methacholine

(Sigma Chemicals, St. Louis, MO, USA) were prepared by dilution in buffered saline (pH 7.4). A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, MD, USA), triggered by a solenoid valve set to remain open for 0.6 s, was used to generate the aerosol from a DeVilbiss 646 nebulizer (DeVilbiss, Somerset, PA, USA), with pressurized air at 13.8 kPa (20 psi). Each subject inhaled five inspiratory capacity breaths of nebulized buffered saline and increasing concentrations of methacholine at 5 min intervals. This gave an output of 0.009±0.0014 mL (mean±SD) per inhalation. FEV_1 was measured at 60–90 s after each inhalation. The inhalation was continued until FEV_1 fell by >20% from the postsaline value. The percentage fall of FEV_1 from the mean postsaline value was plotted against log cumulative dose of inhaled methacholine expressed as breath unit (BU). One BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine. The provocative cumulative dose of methacholine producing a 20% fall in FEV_1 (PD_{20}) was calculated by interpolation between two adjacent data points.

The test that measured wheezing threshold also included breath sound auscultation at baseline and at each stage of serial inhalation. While the children were quietly breathing, the same physician performed breath sound auscultation using a regular paediatric stethoscope for ~30 s beginning just after each measurement of lung function. After the fall in FEV_1 become >20%, the next increment in methacholine was half of the usual amount. The inhalation continued until wheezing was clearly heard over the trachea, or until FEV_1 fell by >50% from the postsaline value, or until three or more data points of highest concentrations fell within a 5% response range, *i.e.*, maximal response plateau occurred [16]. For safety reasons, subjects were given the opportunity to stop the challenge test if they felt too much discomfort. Wheezing threshold was defined as the percentage fall in FEV_1 at the minimal methacholine dose at which wheezing was first detected; whereas it was defined as the final value of percentage fall in FEV_1, if FEV_1 fell by more than 50% or maximal response plateau occurred without wheezing.

The study was approved by the Hospital Ethics Committee, and the parents of the children in the study gave their informed consent.

Statistical analysis

Mean and standard deviation values were calculated for analysis. All PD_{20} values were log-transformed before analysis. Student's t-tests or Wilcoxon rank sum tests were used to analyse the difference in the variables between the two groups. Comparisons of PD_{20} or wheezing threshold between the 2 yrs were analysed for each group, using paired t-tests or Wilcoxon signed rank tests. All of the analyses were made using Stat View II (Abacus Concept Inc., Berkeley, CA, USA) on a Macintosh computer (Apple Computer Inc., Cupertino, CA, USA). A p-value of <0.05 was considered statistically significant.

Results

At the initiation of the study, wheezing threshold and methacholine PD_{20} were compared between CVA (n=36) and CA (n=13) (fig. 1). There was no significant difference in baseline FEV_1 between the two groups (92.9±7.3% predicted *versus* 89.8±9.0% pred) (data not shown). Wheezing was not audible in the provocation procedure with a percentage fall in FEV_1 >50% (two cases of CVA) or with maximal response plateau (five cases of CVA and two cases of CA). With the censored value (last value of percentage fall in FEV_1) in these cases, wheezing threshold was significantly ($p<0.01$) higher in CVA (40.6±7.4%) than in CA (31.3±8.9%). When these cases were excluded from the analysis, the difference was still statistically significant (41.1 ±6.8% in CVA *versus* 31.6±9.6% in CA, $p<0.01$) (data not shown). Geometric mean (range of 1 SD) of methacholine PD_{20} in CVA was 79.8 BU (40.0–159.6), and that in CVA was 60.8 BU (40.5–91.2). This difference did not reach significance ($p=0.10$).

Of the 36 patients with CVA enrolled in the study, seven were lost to follow-up although every effort was made to continue the regular check-ups. Three patients dropped out of the study in the second year; two in the third year; and two in the fourth year. In the year just before drop-out, 4 patients were in cough phase; three were in symptom-free phase. The characteristics of the subjects who completed the study, as well as the patients who were lost, are

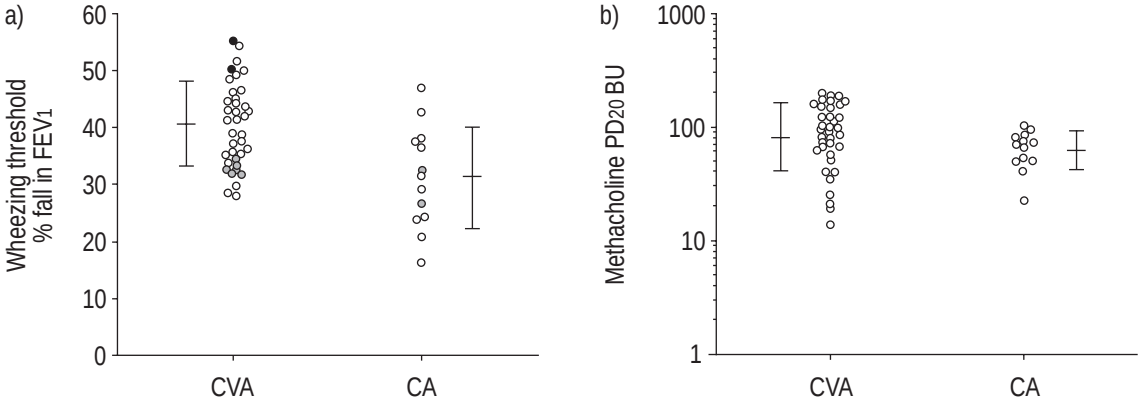

Fig. 1. – Comparison of a) wheezing threshold and b) methacholine provocative cumulative dose producing a 20% fall in forced expiratory volume in one second (FEV_1) (PD_{20}) between cough variant asthma (CVA) (n=36) and classic asthma (CA) (n=13). Mean±1SD are indicated with horizontal bars. ●: fall in FEV_1 >50% without wheezing; ◍: maximal response plateau without wheezing; ○ wheezing threshold; BU: breath unit (one BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine).

summarized in table 1. Those who developed wheezing during the course of follow-up were listed as Group 1; those who did not were listed as Group 2. The patients who dropped out of the study did not significantly differ from those completing the study (Group 1 and 2) with respect to age, sex, prevalence of atopy or FEV_1 level. Methacholine PD_{20} in the initial bronchial provocation test was significantly ($p<0.01$) higher in the drop-out group than in the Groups 1 and 2 combined, whereas wheezing thresholds were similar.

The pattern of symptom presentation and individual PD_{20} in each year during the course of follow-up are presented in table 2. Among the Group 1 patients, 3 subjects developed wheezing in the first year, 4 in the second year, 6 in the third year, and 3 in the fourth year. Among the Group 2 patients, 6 subjects continued to be in cough phase, 5 subjects alternated cough phase with symptom-free phase, and 2 subjects had symptom-free phase during the last 2–3 yrs. The initial PD_{20} values were not significantly different between the two groups. Nine annual PD_{20} data, four in Group 1 and five in Group 2, were not available due to failure to attend the test in the fixed period or due to upper respiratory tract infection within the 4 weeks preceding the test.

Table 2. – The pattern of symptom presentation and individual provocative cumulative dose producing a 20% fall in forced expiratory volume in one second

Subject No.	Initial test	Follow-up			
		1st yr	2nd yr	3rd yr	4th yr
	Group 1				
1	25.0	W 10.2			
2	63.5	W 100.6			
3	81.2	W 58.8			
4	13.8	C 30.6	W 11.2		
5	34.1	C 22.4	W 23.2		
6	39.1	C 38.2	W 14.4		
7	92.7	C 39.6	W 31.5		
8	20.8	C 12.3	C 15.1	W 3.8	
9	50.4	C ND	C 67.2	W 119.9	
10	68.4	C 110.6	C ND	W 23.0	
11	97.6	C 53.7	C 31.3	W 33.4	
12	116.9	C ND	C 234.1	W 40.1	
13	154.7	C 341.5	C 163.9	W 97.6	
14	60.3	C 47.2	C 72.5	C 76.3	W 16.0
15	121.2	C 96.4	C 112.7	C ND	W 171.4
16	169.6	C 145.3	C 198.8	C 155.8	W 67.0
	Group 2				
1	18.6	C 24.6	C 47.8	C 32.0	C 60.5
2	39.7	C ND	C 87.4	C 29.1	C 53.4
3	56.0	C 58.9	C 27.3	C 62.6	C 36.1
4	71.3	C 106.2	C 85.9	F 54.8	C 47.2
5	78.3	C 60.7	F 132.1	C ND	C 33.9
6	84.5	C 101.9	C 80.4	F 142.5	F 105.3
7	88.1	C ND	C 54.5	C 69.3	C 28.8
8	102.9	C 83.6	F 39.7	F 56.6	F 243.4
9	110.4	F 130.6	C ND	C 98.3	F 132.6
10	143.7	C 65.4	C 92.6	C 163.1	C 180.9
11	147.8	C 203.2	F 89.5	C 167.4	C 102.5
12	165.9	C 148.0	C 76.9	C 159.3	C 265.5
13	184.6	C 127.6	C 200.4	F ND	C 120.4

Data presented in breath units (BU; 1 BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine) in each year during the course of follow-up. W: wheezing phase; C: cough phase; F: symptom-free phase; ND: not done.

Among the annual values of PD_{20} in each individual of Group 1, geometric mean (range of 1 SD) of PD_{20} in the years of the wheezing phase (32.8 BU, 11.5–93.3) was significantly ($p<0.01$) lower than the initial values (60.8 BU, 29.2–126.5); however, the values in the years of cough phase (68.9 BU, 27.8–170.6) were not significantly different from the corresponding initial values (72.1 BU, 34.0–153.1) (fig. 2). The changes in PD_{20} between the two consecutive years were assessed according to whether there was a change in symptom presentation. From the years of cough phase to the years of wheezing phase (n=14), a significant decrease in PD_{20} was noted (54.3 BU, 24.0–123.0 *versus* 29.9 BU, 10.8–82.6; $p<0.01$); whereas, between the 2 yrs of cough phase (n=19), no significant change was noted (69.5 BU, 28.4–169.8 *versus* 64.7 BU, 26.1–160.3) (data not shown).

In Group 2, the geometric mean of PD_{20} at the end of study (84.3 BU, 39.7–179.1) was not significantly different from the initial value (85.3 BU, 45.2–161.1). Among the annual values of PD_{20} in each individual, neither the values in the years of cough phase (77.1 BU, 40.9–145.2) nor the values in the years of symptom-free phase (99.1 BU, 57.3–171.4) were different from the corresponding initial values (81.8 BU, 40.8–164.1; 97.5 BU, 78.9–120.5, respectively) (fig. 3). Between the two consecutive years, there was no significant change in PD_{20} either when cough phase was continued (n=30; 77.6 BU, 41.2–146.2 *versus* 77.3 BU, 40.1–148.9) or when cough phase was converted to symptom-free phase (n=7; 96.4 BU, 66.1–140.6 *versus* 93.8 BU, 56.4–156.0) (data not shown). The changes in PD_{20} between the two yrs of symptom-free phase (n=3) or from symptom-free phase to cough phase (n=2) could not be statistically analysed because of the small number.

The changes of wheezing threshold from the initiation to the end of the study are shown in fig. 4. In Group 1, 3 subjects at the initiation and at the end of the study, respectively, necessitated the censored values; in Group 2, 3 subjects at the initiation and two subjects at the end of the study necessitated the censored values. The cumulative dose of methacholine that caused wheezing was significantly different between the two periods in Group

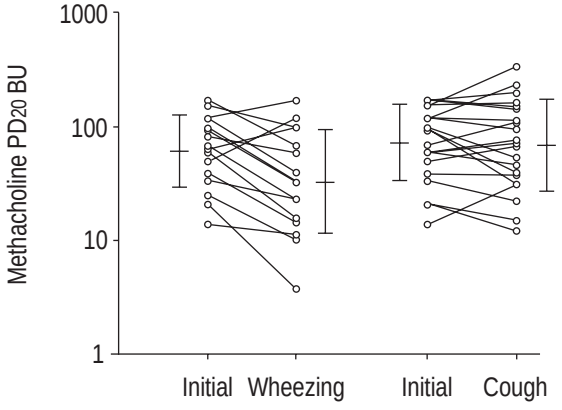

Fig. 2. – The changes of methacholine provocative cumulative dose producing a 20% fall in forced expiratory volume in one second (FEV_1) (PD_{20}) from the initial values to those in the years of the wheezing phase (left) (n=16, $p<0.01$) or to those in the years of the cough phase (right) (n=21, $p=0.68$) among the annual values of PD_{20} in each individual of Group 1. The mean±1SD are indicated with horizontal bars. BU: breath unit (one BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine).

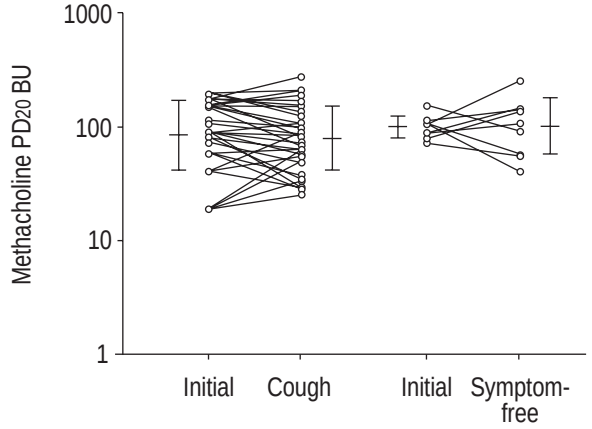

Fig. 3 – The changes of methacholine provocative cumulative dose producing a 20% fall in forced expiratory volume in one second (FEV_1) (PD_{20}) from the initial values to those in the years of the cough phase (left) (n=37, p=0.48) or to those in the years of the symptom-free phase (right) (n=10, p=0.93) among the annual values of PD_{20} in each individual of Group 2. Mean±1SD are indicated with horizontal bars. BU: breath unit (one BU denotes one inhalation of 1 $mg \cdot mL^{-1}$ methacholine).

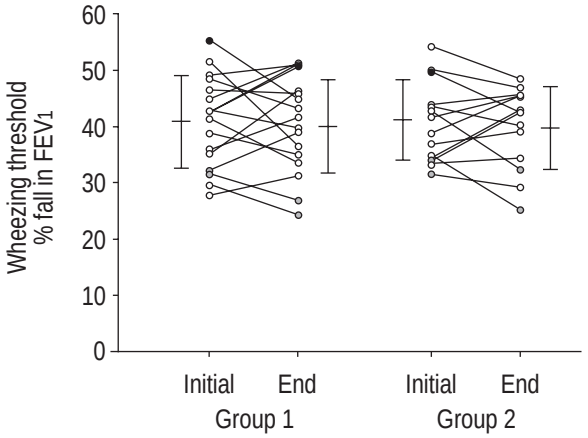

Fig. 4. – The changes of wheezing threshold from the initiation to the end of the study. Mean±1SD are indicated with horizontal bars. There was no significant change either in Group 1 (n=16, p=0.69) or in Group 2 (n=13, p=0.45). ●: fall in forced expiratory volume in one second FEV_1 >50% without wheezing; ◍: maximal response plateau without wheezing; ○: wheezing threshold.

1, but the dose was not different in Group 2 (data not shown). This was not surprising because the subjects in Group 1 showed a deterioration of airway responsiveness at the end of the study, compared with at the initiation of study, *i.e.*, a smaller dose was necessary to provoke the bronchoconstriction. At the initiation of the study, the wheezing thresholds were comparable between the two groups. There was no significant change in wheezing thresholds from the initiation to the end of study either in Group 1 (40.9±8.2% *versus* 40.2±8.3%) or in Group 2 (41.4±7.1% *versus* 40.1±7.3%). The changes were not significant even when the cases necessitating the censored value were excluded (Group 1: 41.2±7.4% *versus* 41.6±6.3%; Group 2: 42.2±6.5% *versus* 42.1±5.8%).

Discussion

In this 4-yr prospective study, it has been shown that airway responsiveness to methacholine increased significantly, but wheezing threshold remained unaltered, as patients with CVA developed wheezing. There was no significant change in either parameter for patients who stayed as CVA or who went on to no longer have asthmatic symptoms.

Some authors [1, 6] have proposed that CVA probably represents the milder end of the spectrum of asthma reflecting a milder degree of airway hyperresponsiveness. CORRAO *et al.* [8] have shown some evidence for this hypothesis through their finding a significantly lower degree of airway hyperresponsiveness in CVA than in CA. However, the simple comparison between the two groups is likely to be biased, because the degree of airway hyperresponsiveness is dependent upon the selection of the CA patients, and the CVA patients may be a heterogeneous group [17]; as exemplified with the current cases, some patients develop the classic signs of asthma, whereas others require no further treatment with resolved cough. In fact, the geometric mean of PD_{20} in the total patients labelled as CVA at the initiation of study tends to be lower, though not statistically significant (p=0.10), than that in CA patients. However, considering the fact that the current authors chose mild asthma patients for the CA group, it is likely that a more balanced group of CA would have shown greater airway hyperreactivity than the CVA group. The results of this study, therefore, do not negate the view that CVA is just one end of the asthma spectrum.

In the present longitudinal study, airway responsiveness to methacholine in patients with CVA significantly increased according to the presence of clinical wheezing. The geometric mean of PD_{20} at the end of wheezing years was significantly lower than the initial values, and 9/-16 patients showed a decrease in PD_{20} of more than a single two-fold concentration of methacholine, a value that is considered to be significant [18]. Furthermore, between the two consecutive years in which cough phase was followed by wheezing phase, a significant reduction of PD_{20} was noted. It is doubted that the increased responsiveness is related to seasonal variation by allergen exposure [19], because each measurement was made in the winter season during which the levels of the relevant allergens for most of the atopic subjects (house dust mites) have been found to be the lowest and the least changing in South Korea [11]. Neither is it likely to result from a possible long-term variability of airway responsiveness, as the authors tried to eliminate supposedly affecting factors such as recent exacerbations [20], viral respiratory infections [21], and exposure to environmental irritants [22]. The increased responsiveness seems to occur neither from variations in baseline airway calibre [23] nor from change in treatment. The baseline FEV_1 as a percentage of the predicted value varied by no more than 10% in each subject; the mean value showed no significant difference between the compared years. Medication added subsequently to the development of wheezing, *i.e.*, inhaled cromolyn sodium or inhaled corticosteroid, would rather modify levels of airway responsiveness. In fact, the mean level of airway responsiveness in Group 2 remained stable for 4 yrs although the level somewhat varied within individual patients. This concurs with the findings in stable mild-to-moderate asthmatics by other

investigators [24]. Although the provocation test was performed in an intentionally blind manner, the grouping of most patients was eventually perceived to the investigator because of the different timing of the test that measured wheezing threshold. It is not, however, considered to be a drawback because methacholine PD_{20} is an objective test.

The concept of wheezing threshold is based on an individual variation in the severity of airway obstruction at the presence of wheezing [25]. By showing that wheezing threshold, measured at the initiation of study, is higher in patients with CVA as a whole than it is in patients with CA, the findings of a previous study have been confirmed [5]. The simple comparison of percentage fall in FEV_1 at wheezing may not be strictly fair because wheezing could have been heard at a concentration of methacholine lying between the current and the previous one. However, the authors do not believe that their findings are due to overestimation of wheezing threshold for the CVA group, *i.e.*, wheezing had occurred with the FEV_1 closer to that at one previous concentration. Baseline airway calibre may influence the level of the wheezing threshold because the level is measured as a percentage fall from the baseline value. There was, however, no significant difference in baseline FEV_1 as a percentage of predicted value between the two compared groups. The censored value, which was adopted when wheezing was not audible in the stepwise airway narrowing procedure, implies an underestimation of the wheezing threshold. However, this approach would not significantly affect the comparison. In fact, the difference between the two groups was still significant when those cases were excluded from the analysis.

Over the years of the follow-up, wheezing threshold level did not change significantly in patients with CVA. The factors discussed above might have complicated the comparison, but baseline FEV_1 and the number of cases necessitating the censored value were similar between the two periods for each studied group. The maintenance of the wheezing threshold at a higher level in patients who were converted from CVA to CA (Group 1) as well as in patients who stayed as CVA or who came to no longer have asthmatic symptoms (Group 2) suggests that the development of wheezing in patients with CVA is not associated with a decrease in the wheezing threshold. Now that a higher wheezing threshold is found in CA patients who are converted from CVA than that in those who have the same type of disease all along, it is not the unique characteristic of CVA. It is proposed that the degree of the wheezing threshold as an individual trait may determine the pattern of symptom development in asthma. Another inference that can be drawn from the results is that the presence of wheezing in patients who previously experienced CVA may imply more severe airway obstruction than that in patients who did not.

The mechanism by which the development of wheezing in patients with cough variant asthma is associated with an increase in airway hyperresponsiveness is not clear but speculative. Previous studies have shown a significant inverse correlation between methacholine or histamine threshold value and peak expiratory flow rate (PEF) variability in asthmatic subjects [26] as well as in subjects with episodic cough, dyspnoea or wheezing who showed mild to moderate hyperresponsiveness [27]. A significant correlation was more recently detected between the severity of airway responsiveness and the parameter of isolated or short-term reductions in PEF [28]. Thus, patients with a mild increase in airway responsiveness may have a mild increase in variability of airflow obstruction; they will report cough but not wheeze if the degree of airway narrowing is not sufficient for the development of wheezing. Longitudinal observation of children with recurrent cough or wheeze indicates that episodes of cough or wheeze may be associated with falls in PEF. However, children with wheeze have greater PEF variability and increased prevalence of airway hyperresponsiveness [29]. One study of asthma exacerbation induced by corticosteroid withdrawal indicated that symptoms could deteriorate before changes in PEF, and that cough could be one of the first signals of asthma exacerbation in this setting [30].

Although the increase in airway responsiveness in patients with CVA paralleled the development of wheezing as a whole in Group 1, it should be noted that some patients exhibited no change or even a decrease. One possible explanation of this is that the severity of airflow obstruction in asthma may be determined by the interaction of airway responsiveness and the strength of a bronchoconstriction stimulus [31]. Thus, changes in the state of asthma might rather be the result of variation in the latter than in the former.

In conclusion, the increased degree of airway hyperreactivity during the course of cough variant asthma may have a pathogenetic role in the development of wheezing, probably *via* increased variability of airflow obstruction. This strengthens the suggestion that different expressions of those factors that contribute to development and maintenance of airway disease place each child on a different part of the asthma spectrum and as a consequence lead to the observed difference in the manifestation of the disease [32].

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